

From the INTERNATIONAL SEARCHING AUTHORITY

To:
 IVOR R. ELRIFI
 MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO
 P.C.
 ONE FINANCIAL CENTER
 BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing (day/month/year)	
Applicant's or agent's file reference 17811-017CIP	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US03/27888	International filing date (day/month/year) 05 September 2003 (05.09.2003)
Applicant ISOTIS SA	

1. The applicant is hereby notified that the international search report has been established and transmitted herewith.

Filing of amendments and statements under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO website.

RECEIVED

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	DEC 08 2003	Authorized officer Christopher Nichols, Ph.D. Telephone No. 703-308-0196
MINTZ LEVIN, BOSTON PATENT DOCKET DEPT.		

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
 IVOR R. ELRIFI
 MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEL
 P.C.
 ONE FINANCIAL CENTER
 BOSTON, MA 02111

<input type="checkbox"/> File Folder	Done By 2/1/04
<input checked="" type="checkbox"/> Data Entry	
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<input type="checkbox"/> Annuities	

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

04 DEC 2003

Applicant's or agent's file reference
 17811-017CIP

Date of Mailing
 (day/month/year)

International application No.
 PCT/US03/27888

FOR FURTHER ACTION See paragraphs 1 and 4 below

International filing date
 (day/month/year)

05 September 2003 (05.09.2003)

Applicant
 ISOTIS SA

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See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
 Mail Stop PCT, Attn: ISA/US
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 Facsimile No. (703)305-3230

Authorized officer
 Christopher Nichols, Ph.D.
 Telephone No. 703-308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 17811-017CIP	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/27888	International filing date (day/month/year) 05 September 2003 (05.09.2003)	(Earliest) Priority Date (day/month/year) 06 September 2002 (06.09.2002)
Applicant ISOTIS SA		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (See Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

PCT/US03/27888

Continuation of B. FIELDS SEARCHED Item 3:

WEST (USPT, PGPUBS, JPO, EPO, DERWENT); NCBI (PUBMED); STN (BIOSCIENCE)
fibroblast, keratinocyte, differentiated, differentiation, fibrin, collagen, matrix, allogeneic, epithelial, blood, mitomycin C, X-ray, scaffold, wound dressing, T antigen, EBV, HTLV-1, EBNA2, glycerol, c-myc, c-kun. myc, n-myc

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/27888

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 35/00, 48/00; C07K 5/00, 14/00; C12N 15/85, 15/86
US CL : 424/93.1; 435/325; 514/44; 530/300, 350, 399

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/93.1; 435/325; 514/44; 530/300, 350, 399

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ✓	US 5,891,558 A (BELL et al.) 06 April 1999 (06.04.1999), Cols. 4-19.	1-91
X ✓	US 5,855,617 A (ORTON) 05 January 1999 (05.01.1999), Cols. 4-6.	1-91
X ✓	US 5,863,296 A (ORTON) 26 January 1999 (26.01.1999), Cols. 4-7.	1-91
X,P ✓	US 2003/0064927 A1 (GESTRELIUS et al.) 03 April 2003 (03.04.2003), Examples 1-9.	1-91
X,P ✓	US 2003/0166274 A1 (HEWITT et al.) 04 September 2003 (04.09.2003), Examples I-IX.	1-91
X ✓	COOPER, M.L. et al. Use of a composite skin graft composed of cultured human keratinocytes and fibroblasts and a collagen-GAG matrix to cover full-thickness wounds on athymic mice. <i>Surgery</i> . February 1991, Vol. 109, No. 2, pages 198-207, especially Figures 1 and 4, Table I.	1-91



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"E" earlier application or patent published on or after the international filing date

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"O" document referring to an oral disclosure, use, exhibition or other means

"&"

document member of the same patent family

"P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

31 October 2003 (31.10.2003)

Date of mailing of the international search report

04 DEC 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
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Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer

Christopher Nichols, Ph.D.

Telephone No. 703-308-0196

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ✓	LANGDON, R.C. et al. Reconstitution of Structure and Cell Function in Human Skin Grafts Derived from Cryopreserved Allogeneic Dermis and Autologous Cultured Keratinocytes. <i>J Invest Dermatol.</i> November 1988, Vol. 91, No. 5, pages 478-485, especially Figures 1-4.	1-91
X ✓	SUGIHARA, H. et al. Effects of fat cells on keratinocytes and fibroblasts in a reconstructed rat skin model using collagen gel matrix culture. <i>British Journal of Dermatology.</i> 2001, Vol. 144, pages 244-253, especially Figures 1 and 2.	1-91
X ✓	KOLODKA, T.M. et al. Evidence for keratinocyte stem cells in vitro: Long term engraftment and persistene of transgene expression form retrovirus-transfected keratinocytes. <i>Proc. Natl. Acad. Sci., USA.</i> April 1998, Vol. 95, pages 4356-4361, especially Table 1 and 2.	1-91
X ✓	BADIAVAS, E. et al. Retrovirally mediated gene transfer in a skin equivalent model of chronic wounds. <i>Journal of Dermatological Science.</i> 1996, Vol. 13, pages 56-62, especially Figure 3.	1-91
X ✓	MARUGUCHI, T. et al. A new skin equivalent: Keratinocytes proliferated and differentiated on collagen sponge containing fibroblasts. <i>Plast. Reconstr. Surg.</i> March 1994, Vol. 93, No. 3, pages 537-546, especially Figures 1-4.	1-91
A,P ✓	US 2002/0169105 A1 (GESTRELIUS et al.) 14 November 2002 (14.11.2002), entire document.	1-91
A ✓	US 2002/0031500 A1 (MACLAUGHLIN et al.) 14 March 2002 (14.03.2002), entire document.	1-91
A ✓	KUROYANAGI, Y. et al. A cultured skin substitute composed of fibroblasts and keratinocytes with a collagen matrix: Preliminary results of clinical trials. <i>Ann Plast Surg.</i> October 1993, Vol. 31, No. 4, pages 340-351, entire document.	1-91
A ✓	DEL RIO, M. et al. A preclinical model for the analysis of genetically modified human skin in vivo. <i>Human Gene Therapy.</i> 20 May 2002, Vol. 13, No. 8, pages 959-968, entire document.	1-91
A ✓	CURRIE, L.J. et al. The use of fibrin glue in skin grafts and tissue-engineered skin replacements: A Review. <i>Plast Reconstr Surg.</i> November 2001, Vol. 108, No. 6, pages 1713-1726, entire document.	1-91